

REMARKS

Claims 1-5, 8, 11-17, 22-24 and 27 were pending prior to entering the amendments.

The Amendments

Claim 1 is amended to change the wherein clauses to active steps.

Claims 2 and 8 are cancelled.

Claims 23 and 27 are amended to clarify the claim language.

No new matter is added in any of the amendments. The Examiner is requested to enter the amendment and reconsider the application.

Telephone Interview

Applicants are grateful to Examiner Dr. Aeder and Supervisor Ms. Yu for the courtesy telephone interview dated March 11, 2008. During the telephone interview, it was agreed that Applicants would amend Claim 1 to change the wherein clauses to active steps such that the claim limitation would be considered favorably.

Applicants have amended Claim 1 to recite step (d), characterizing the simultaneous presence of cells expressing the high risk HPV gene-product and cells overexpressing p16^{INK4a} as indicative of neoplastic or dysplastic lesion, and step (e), characterizing the presence of cells overexpressing p16INK4a alone as indicative of metaplasias.

Since the Amendment dated January 16, 2008 was not entered, Applicants are repeating the arguments as follows.

The Present Invention

Metaplasia

The dictionary definition of metaplasia is abnormal replacement of cells of one type by cells of another (see Merriam Webster's Collegiate Dictionary, 10th Edition, 1997, page 731, copy attached). The cervix is located between the vagina and the uterus. The vaginal epithelium is squamous epithelium, and the uterine epithelium is columnar epithelium. The cells in the cervical area can undergo the transformation of one type of mature differentiated cell type into another mature differentiated cell type (squamous to columnar, or columnar to

squamous). In this stage of cellular differentiation, the cells are called metaplastic cells. The morphology of metaplastic cells resembles immature cells and it is not dissimilar from the morphology of dysplastic cells. Metaplasia is not considered carcinogenesis and it is important to discriminate metaplasia from pre-cancerous or cancerous lesions.

The present invention identifies the problem that about 30% of metaplastic cells show some immunoreactivity with p16^{INK4a} specific antibodies, and could lead to false-positive results in mataplasia cells (page 1, lines 20-21). This unique problem exists only in the cytological (cell-type) testing, and is not a problem in histological (tissue-type) testing. A positive result of p16 of metaplastic cells in histological testing is not a problem because the availability of the tissue-based morphological information. However, in cytological testing such as by Pap smear, the tissue information does not exist and thus a positive result of p16 in metaplastic cells is indeed a problem for diagnosis.

None of the cited prior art has either identified the problem, let alone provided a solution.

The Present Claims

The present invention provides a method for discriminating p16^{INK4a} overexpressing metaplasias from p16^{INK4a} overexpressing neoplastic or dysplastic lesions in a uterine cervix sample in the course of cytological testing procedures. The discrimination method is based on the presence or absence of (a) cells expressing a high risk HPV gene-product and (b) cells overexpressing p16^{INK4a} in the same uterine cervix sample.

The Response

35 USC §103(a) Rejection

Claims 1-3, 8, 11-17, 22-24 and 27 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Klaes et al. (2001, Int. J. Cancer 92:276-284) in view of Solomon et al. (2001, J. of the National Cancer Institute 93(4):293-299) and Guccione (Virology 293:20-25 (2002)), as evidenced by von Knebel Doeberitz (2001, Dis. Markers 17(3):123-8 (abstract only)). The rejection is traversed because none of the prior art has disclosed a need to improve the specificity of p16 in a cytological testing procedure.

Klaes et al.

Klaes et al. report that “p16^{INK4a} is a specific biomarker to identify dysplastic and neoplastic cervical epithelia in sections of cervical biopsy samples or cervical smears.” (see last sentence of Abstract and Title). Klaes et al. do not describe any problems with the p16 staining when used in cytology. Klaes et al. do not recognize the problem that about 30% of metaplastic cases show some immunoreactivity with p16^{INK4a} specific antibodies and that measuring p16^{INK4a} alone cannot discriminate metaplasia from neoplasia in Pap smear.

Claim 1 is directed to a method for discriminating p16^{INK4a} overexpressing metaplasias from p16^{INK4a} overexpressing neoplastic or dysplastic lesions in a uterine cervix sample in the course of cytological testing procedures, by characterizing the simultaneous presence of cells expressing the high risk HPV gene-product and cells overexpressing p16^{INK4a} as indicative of neoplastic or dysplastic lesion, and characterizing the presence of cells overexpressing p16^{INK4a} alone as indicative of metaplasias. Clearly, Klaes et al. failed to disclose the above-recited claim limitation.

A person skilled in the art reading Klaes et al. would understand that p16 is a sensitive and specific biomarker in the cytological testing and there is no need to search for another marker to improve the specificity of the test.

Solomon et al.

1. Solomon et al only disclose a test for HPV infection.

Solomon et al disclose testing HPV DNA (hc2) in solubilized cell samples, in women referred to colposcopy. Solomon et al. tested HPV DNA by solubilizing the cells; Solomon et al did not test HPV protein or use a cytological testing procedure. The hc2 test is a nucleic acid based test performed on lysed swab material, not on a cellular level. The hc2 test detects the nucleic acid of HPV, which indicates the infection with HPV. However, a high percentage of infection regresses and does not lead to oncogenic transformation. Therefore, the hc2 testing cannot discriminate metaplastic cells from dysplastic or neoplastic cells.

2. Solomon et al do not disclose testing cells expressing a high risk HPV gene-product.

After HPV infection, a high risk HPV gene-product such as E7 protein needs to be expressed in cells to induce and uphold oncogenic transformation. Solomon et al only disclose a test for the HPV infection, but do not disclose testing the E7 protein. As a matter of fact, at the time of this invention, there was no information on immunocytochemical testing of E7 in a uterine cervix sample.

3. A person skilled in the art would not have selected the combination of p16 with E7.

There is no hint in Solomon et al. that the HPV DNA testing should be combined with another testing of a different immunochemical marker. Even if there is any hint in Solomon et al, a person skilled in the art would not have selected the combination of p16 with E7 for the following reasons.

There are numerous markers for which immunohistochemistry testing on cervical lesions has been reported (claudin, p53, hTERT, Fhit, mcm2, cdc4, mcm5, p21, p27, c-Erb2, Id1, bcl2, bax, integrin Alpha6, Muc2, Ki67, Cyclin E, Cyclin D1, Cyclooxygenase2, telomerase, E-cadherin, etc.). However, E7 was not reported for immunocytochemical testing in a uterine cervix sample prior to the present invention. There was no information on useful combinations in the art prior to the present invention.

The expression of the two proteins p16 and HPV E7 is closely interrelated. Von Knebel Doeberitz (*Dis Markers*, 17:123-8, 2001, cited by the Examiner) reports that “Expression of two viral oncogenes, E6 and E7, in epithelial stem cells is required to initiate and maintain cervical carcinogenesis and results in significant overexpression of the cellular p16^{INK4a} protein.” P16 is regarded as a cellular substitute marker to show oncogenic transformation with HPV E7. A person skilled in the art would have considered that the p16 and E7 markers are redundant, and that the combination of them would not render any additional information.

Guccione et al.

Guccione only teaches detection of recombinant HPV E7 protein that have been genetically modified to bear a haemagglutinin tag for enhanced detection. Guccione et al. do not mention p16^{INK4a} at all or provide a method for discriminating p16 overexpressing metaplasias from p16 overexpressing neoplastic or dysplastic lesions. Guccione et al. do not

cure the deficiency of Klaes et al. and Solomon et al.

Reduction to Practice

Klaes et al. identify p16^{INK4a} as a specific biomarker. Klaes et al. do not recognize the false-positive problem of p16^{INK4a} in metaplastic cells. Reading Klaes et al., a person skilled in the art would have no reason to combine another biochemical marker with p16^{INK4a} to improve the specificity of the test, which discriminates metaplasia from dysplasia and neoplasia.

The cited references neither discovered the problem nor provided a solution to the problem. Applicants have discovered that two related biochemical markers of p16^{INK4a} and the high risk HPV gene-product are not redundant and are complementary for discriminating metaplasias from neoplastic or dysplastic lesions. Applicants have reduced the invention to practice. In Example 1, cells originating from metaplasias were stained by the immunoreaction specific for p16, but not stained by the immunoreaction specific for the HPV E2 protein or HPV L1 protein; whereas dysplastic cells were stained by both p16 and E2/L1. In Example 3, cells originating from metaplasias were stained by the immunoreaction specific for p16, but not stained by the immunoreaction specific for the HPV E7 protein; whereas neoplastic cells were stained by both p16 and E7.

Objections

Claims 2 and 8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 2 and 8 are cancelled.

Claim 23 is objected to because of an apparent typographical error. Claim 23 is amended according to the Examiner's suggestion.

Claim 27 is objected to because there appears to be text missing between "cells" and "high". Claim 27 is amended according to the Examiner's suggestion.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. Early notification of allowance is earnestly solicited.

Respectfully submitted,

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Enclosure: Merriam Webster's Collegiate Dictionary, 10th Edition, 1997, page 731

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meta-physic \mē-tä-fiz'ik\ n [ME *metaphysyke*, fr. ML *metaphysica*] [*late Lat.* = **METAPHYSICS *b*: a particular system of metaphysics]**

a: the system of principles underlying a particular study or subject

metaphysic \mē-tä-fiz'ik\ adj

metaphysic \mē-tä-fiz'ik\ n [L *metaphysica*] 1 : of or relating to metaphysics

a : of or relating to the transcendental or to a reality beyond what is perceptible to the senses

b : supernatural 3 : highly abstract or elusive; also: THEORETICAL 4 often cap: of or relating to poetry esp. of the early 17th century that is highly intellectual and philosophical and marked by unconventional imagery — **meta-physical**

adj — **meta-physics \mē-tä-fiz'iks\ n** [ME *metaphysyke*] a: a metaphysical poet of the 17th century

b: a student of or specialist in metaphysics

meta-physi-cian \mē-tä-fiz'ē-shən\ n [15c] : a student of or specialist in metaphysics

meta-physi-cism \mē-tä-fiz'ik-siz\ n [15c] constr [ML *Metaphysica*, title of Aristotle's treatise on the subject, fr. Gr. *meta* (*ta physika*) *liter* (the works) + the physicks] 1: the treatment of metaphysics in its traditional works [15c] 2: a division of philosophy that is concerned with the fundamental nature of reality and being and that includes ontology, cosmology, and often epistemology (2) : ONTOLOGY 2 b: abstract philosophical studies: a study of what is outside objective experience

meta-physi-cist \mē-tä-fiz'ik-sit\ n [1610] 1: transformation of one type into another 2: abnormal replacement of cells of one type by those of another — **meta-plastic \plä-stik\ adj**

meta-physi-colog \mē-tä-fiz'ik-lōj\ n [15V] (ca. 1909) : speculative psychology concerned with postulating the structure (as the ego and id) and processes (as cathexis and projection) of the mind and with observing their relations

meta-physi-cology \mē-tä-fiz'ik-lōj\ n [ca. 1924] 1: any of a genus (*Metasequoia*) of fossil and living coniferous trees of the bald cypress family that have leaves, buds, and branches arranged oppositely and flat leaves resembling needles

meta-physi-cism \mē-tä-fiz'ik-siz\ n [1866] : metamorphosis that involves changes in the chemical composition as well as in the texture of rock — **meta-so-matic \mē-sō-mat'ik\ adj**

meta-sta-bile \mē-tä-bil\ adj [ISV] (1897) : having or characterized by only a slight margin of stability (as a compound) — **meta-sta-bil-i-ty \mē-tä-bil'i-tē\ n** [ca. 1924] 1: metastable 2: *a* : a secondary metastatic growth of a malignant tumor — **meta-sta-tic \mē-tä-stä-tik\ adj** — **meta-sta-ti-cally \mē-tä-stä-ti-käl\ adv** — **meta-sta-size \mē-tä-stä-siz\ v** [-sized; -siz-ing] (1907) : to spread by or as if by metastasis

meta-star-tar \mē-tä'star-tär\ adj (1739) : of, relating to, or being the part of the human foot or of the hind foot in quadrupeds between the tarsus and the angles

meta-tar-sus \mē-tä-tär'süs\ n [NL] (1676) : the metatarsal part of a human foot or of a hind foot in quadrupeds

meta-tea \mē-tä'tē\ n [Sp. *fr. Latin* *metacal*] (1834) : a stone with a concave upper surface used in the lower molars for grinding grains and esp. coffee

meta-tha-sis \mē-tä-thä'sis\ n [Gr. *meta*- + *thesis* to place — more at *STAND*] (1663) : change of position or condition: as a: a transfer of a disease-producing agency from the site of disease to another part of the body b: a secondary metastatic growth of a malignant tumor — **meta-tha-static \mē-tä-thä-tä-tik\ adj** — **meta-tha-ti-cally \mē-tä-thä-ti-käl\ adv** — **meta-tha-size \mē-tä-thä-siz\ v** [-sized; -siz-ing] (1907) : to spread by or as if by metastasis

meta-tha-tar-sal \mē-tä'tär-tär-säl\ adj (1739) : of, relating to, or being the part of the human foot or of the hind foot in quadrupeds between the tarsus and the angles

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meta-tha-sis \mē-tä-thä'sis\ n [Gr. *meta*- + *thesis* to place — more at *STAND*] (1663) : change of place or condition: as a: a transposition of two phonemes in a word (as in the development of *crud* from *curd* or the pronunciation *'pü-rë* for *pretty*) b: a chemical reaction in which different kinds of atoms exchange positions to form other kinds of molecules — **meta-tha-ter-ic \mē-tä-thä-tërik\ adj** or **meta-tha-thetic \mē-tä-thä-ti-tik\ adj** — **meta-tha-ter-ic-ally \mē-tä-thä-tërik-äl\ adv**

meta-tha-ro-lic \mē-tä-thä-rö'lik\ adj (ca. 1839) : of, relating to, or situated in or on the metathorax *(= test)*

meta-tha-tox \mē-tä-thäk' \ n [ca. 1816] : the posterior segment of the thorax of insects — see *insect* illustration

meta-xylem \mē-täk'leäm\ n [Jlem] (n 1902) : the part of the primary xylem that differentiates after the protoxylem and that is distinguished typically by broader tracheids and vessels with pitted or reticulate walls

meta-zo-an \mē-zö'än\ n [NL *Metazoa*, fr. *meta*- + *zoa*] (1884) : any of a group (*Metazoa*) that comprises all animals having the body composed of cells differentiated into tissues and organs and usu. a digestive cavity lined with epithelial cells — **meta-zoan \mē-zö'än\ adj**

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me-to-or-ite \mē-tōr'ē-it\ n (1811) : a meteor that reaches the surface of the earth without being completely vaporized — **me-to-or-itic** [*late Lat.* = *meteoro-nik* *a*; also *me-to-or-i-tic* *cal* *v-ik-ti-nik* *ad*] *a*: of or relating to meteors

me-to-or-ite \mē-tōr'ē-it\ n (1811) : a meteorite in which the mineral *meteoroite* is the dominant mineral — **me-to-or-ite** [*late Lat.* = *meteoro-ite* *n* *fr. OE* *mētēr* *fr. L* *metrum*, fr. *Gk* *metron* measure, meter] *a*: more at **MEASURE**

me-to-or-ite \mē-tōr'ē-it\ n (1811) : a systematically arranged and measured rhyme in verse: 1: *i* : rhyme that continuously repeats a single basic pattern (ambic) 2: *ii* : rhyme characterized by regular recurrence of patterns in the arrangement of the letters in large figures (ballad) — **me-to-or-ite** [*i* : a measure of unit metrical value] *a*: a measure of unit metrical value in a poem or song — **me-to-or-ite** [*ii* : a fixed metrical pattern] *a*: a fixed metrical pattern of note values, accents, and beats per measure

me-to-or-ite \mē-tōr'ē-it\ n (1811) : a fixed metrical pattern of note values, accents, and beats per measure

me-to-or-ite \mē-tōr'ē-it\ n (1811) : a fixed metrical pattern of note values, accents, and beats per measure

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